FORM PTO-1390 (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: 146.1375

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/018073

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR00/01568	June 8, 2000	June 9, 1999

TITLE OF INVENTION: NEW DERIVATIVES OF ECHINOCANDINE, THEIR PREPARATION PROCESS AND THEIR USE AS ANTIFUNGALS

APPLICANT(S) FOR DO/EO/US: FAIVEAU et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [X] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: French International Preliminary Examination Report; PCT/IB/306

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/018073	PCT/FR00/01568	146.1375

	CALCULATIONS PTO USE ONLY
17. [X] The following fees are submitted:	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00	$1040.00
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$1040.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	18 - 20 =	0	X $18.00	$ 1040.00
Independent claims	1 - 3 =	0	X $78.00	$
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 1040.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				$ 1040.00
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 1040.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$ 1040.00
			Amount to be: refunded	$
			charged	$

a. [X] ~~A check in the amount of $~~ PTO Form 2038 is enclosed. ~~to cover the above fees is enclosed.~~

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275 . A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Bierman, Muserlian and Lucas
600 Third Avenue
New York, NY 10016

Charles A. Muserlian
SIGNATURE:

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Our Ref.: 146.1375

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
FAUVEAU et al
PCT/FR00/01568 : PCT Date: June 8, 2000
Serial No.:
Filed: Concurrently Herewith
For: NEW DERIVATIVES...AS ANTI-FUNGALS

600 Third Avenue
New York, NY 10016
December 4, 2001

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

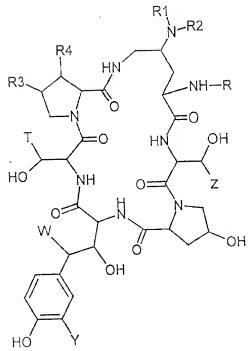
IN THE SPECIFICATION:

Page 1, before line 1, insert

--This is a 371 of PCT/FR00/01568 filed on June 8, 2000.--

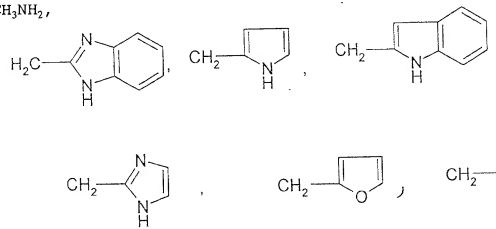
IN THE CLAIMS:

Claim 1 (amended) A compound selected from the group consisting of all possible isomeric forms and their mixtures, a compound of the formula



(I)

either R_1 is hydrogen or methyl and R_2 is selected from the group consisting of cyclohexyl substituted by an amine, $CH_2CH_2NHCH_3$, $CH_2CHCH_3NH_2$,



$CHCH_3CH_2NH_2$, -(CH2)aOH where a is an integer of 1 to 8, (CH_2)b-C≡N where

b is an integer of 1 to 8, $CHCH_3C_6H_5$, (CH_2)-$C(CH_3)_2NHCOCF_3$, and $CHCH_3(CH_2)$dOH where d is an integer of 1 to 8

or R_1 and R_2 together with the nitrogen to which they are attached

form a ring of 3, 4 or 5 carbons optionally substituted by an amine

R_3 is selected from the group consisting of hydrogen, methyl and hydroxyl

R_4 is hydrogen or hydroxyl,

R is selected from the group consisting of alkyl and cycloalkyl of up to 30 carbon atoms, optionally containing at least one heteroatom, at least one heterocycle and alkyl or cyclic acyl of up to 30 carbon atoms optionally containing at least one heteroatom, and/or at least one heterocycle,

T is selected from the group consisting of hydrogen, methyl, $-CH_2CONH_2$, $-CH_2C{\equiv}N$, $-(CH_2)_2NH_2$ and $-(CH_2)_2Nalk^+X^-$, X is halogen and alk is alkyl of up to 8 carbon atoms,

Y is selected from the group consisting of hydrogen, hydroxyl, halogen and $-OSO_3H$ or the salt thereof,

W is hydrogen or OH,

Z is hydrogen or methyl and its non-toxic, pharmaceutically acceptable acid addition salt.

Claim 2 (amended) A compound of claim 1 in which T is hydrogen.

Claim 3 (amended) A compound of claim 1 in which W is hydrogen.

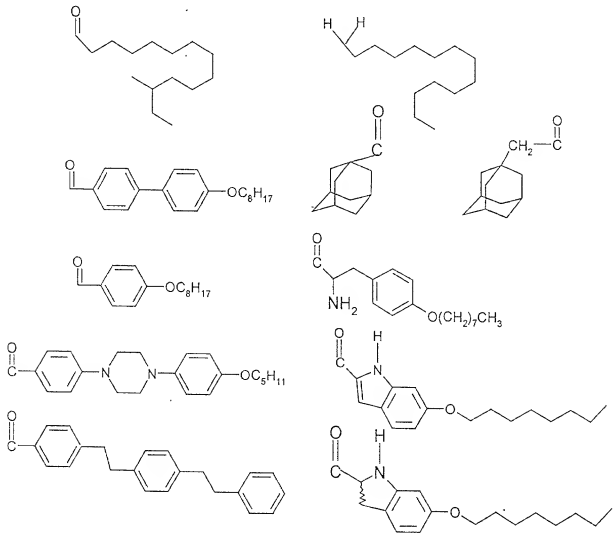
Claim 4 (amended) A compound of claim 1 in which Z is methyl.

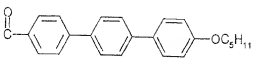
Claim 5 (amended) A compound of claim 1 in which Y is hydrogen.

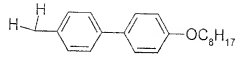
Claim 6 (amended) A compound of claim 1 in which R_3 is methyl.

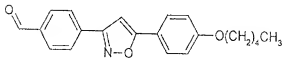
Claim 7 (amended) A compound of claim 1 in which R_4 is hydroxyl.

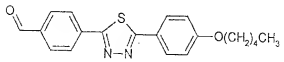
Claim 8 (amended) A compound of claim 1 in which R is selected from the group consisting of

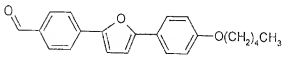


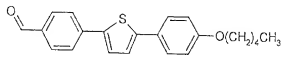




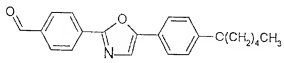




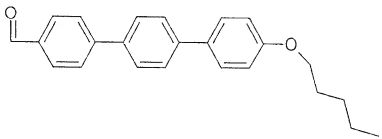




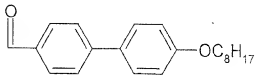
and



Claim 9 (amended) A compound of claim 8 in which R is

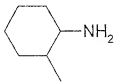


Claim 10 (amended) A compound of claim 8 in which R is

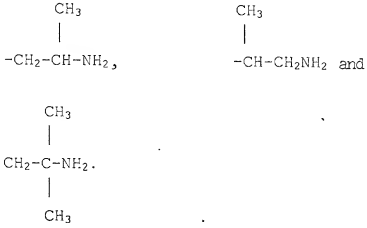


Claim 11 (amended) A compound of claim 1 in which R_1 is hydrogen.

Claim 12 (amended) A compound of claim 1 in which R_2 is



Claim 13 A compound of claim 1 in which R_2 is selected from the group consisting of



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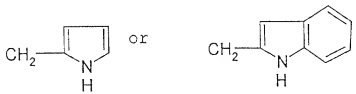
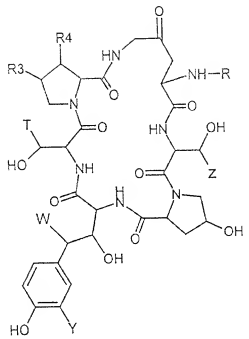
Claim 14 (amended) A compound of claim 1 in which R2 is



Claim 15 (amended) A compound of claim 1 selected from the from the group consisting of

- 1-[4-[[(1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B), and
- trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl-carbonyl]-L-ornithine]-4-[4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

Claim 16 (amended) A process for the preparation of a compound of claim 1 comprising reacting a compound of the formula



(II)

wherein R, R_3, R_4, T, Y, W and Z are defined as in claim 1 with an amine or amine derivative capable of introducing

in which R_1 and R_2

are defined as in claim 1 and optionally to the action of a reducing agent

and/or an amine functionalization agent,

and/or an acid to form the salt of the product of claim 1,

and/or a separation agent of the different isomers obtained.

Cancel claims 17 and 18 and add the following claims.

--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

Charles A. Muserlian, #19,683
Attorney for Applicant(s)
Tel. # (212) 661-8000

CAM:sd
Enclosure: Return Receipt Postcard

--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

Charles A. Muserlian, #19,683
Attorney for Applicant(s)
Tel. # (212) 661-8000

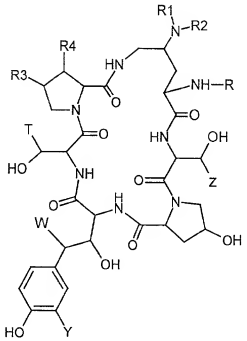
CAM:sd
Enclosures: Marked-Up Version of Specification and Claims
Return Receipt Postcard

New derivatives of echinocandine, their preparation process and their use as antifungals.

-- This is a 371 of PCT/FR00/01568 filed June 8, 2000.--

The present invention relates to new derivatives of echinocandine, their preparation process and their use as antifungals.

A subject of the invention is, in all possible isomer forms as well as their mixtures, the compounds of formula (I):

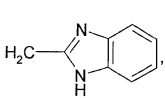


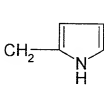
(I)

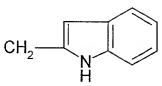
in which

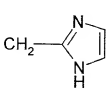
either R_1 represents a hydrogen atom or a methyl radical.

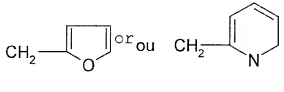
R_2 represents a cyclohexyl radical substituted by an amine, a $CH_2CH_2NHCH_3$ radical, a $CH_2CHCH_3NH_2$ radical, a







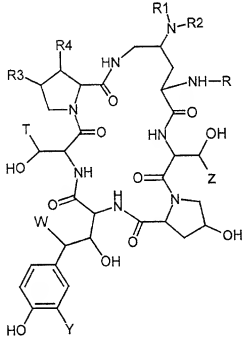




radical, a $CHCH_3CH_2NH_2$ radical, a $-(CH_2)aOH$ radical, a

A compound selected from the group consisting of

1) ~~In~~ all possible isomeric forms ~~as well as~~ and their mixtures, ~~the~~ compounds of the formula ~~(I):~~

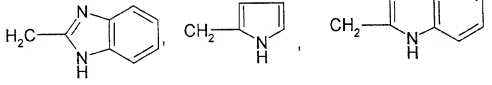


(I)

~~in which~~

either R_1 ~~represents a~~ is hydrogen ~~atom~~ or methyl ~~radical,~~ and

R_2 ~~represents a~~ cyclohexyl ~~radical~~ substituted by an amine, a $CH_2CH_2NHCH_3$ ~~radical~~, a $CH_2CHCH_3NH_2$ ~~radical~~, a is selected from the group consisting of



~~radical~~, a $CHCH_3CH_2NH_2$ ~~radical~~, a -(CH2)aOH wherein ~~radical~~, a ~~representing~~ an integer ~~comprised between~~ of 1 ~~and~~ to 8, a $(CH_2)b$-C≡N wherein ~~radical~~ b ~~representing~~ is an integer ~~comprised between~~ of 1 ~~and~~ to 8, a $CHCH_3C_6H_5$ ~~radical~~, a (CH_2)-$C(CH_3)_2NHCOCF_3$ ~~radical~~, and

$CHCH_3(CH_2)$dOH ~~radical~~, d ~~representing~~ an integer ~~comprised between~~ 1 ~~and~~ 8

or R_1 and R_2 together with the nitrogen ~~which carries them~~ form a ring ~~of~~ 3, 4 or 5 carbons optionally substituted by an amine

R3 ~~represents a~~ hydrogen ~~atom~~, ~~a~~ methyl ~~or~~ hydroxyl ~~radical~~,

R_4 ~~represents a~~ hydrogen ~~atom~~ or ~~a~~ hydroxyl ~~radical~~

R^* ~~represents~~ a linear or branched ~~or~~ cyclic ~~acyl radical containing~~ up to 30 carbon atoms, optionally containing one ~~or more~~ heteroatom~~s~~, one ~~or more~~ heterocycle~~s~~ or cyclic acyl ~~radical containing~~ up to 30 carbon atoms optionally containing one ~~or more~~ heteroatom~~s~~ and/or one ~~or more~~ heterocycle~~s~~,

T ~~represents a~~ hydrogen ~~atom~~, ~~a~~ methyl ~~radical~~, ~~a~~ $-CH_2CONH_2$, $-CH_2C{\equiv}N$ ~~radical~~, ~~a~~ $-(CH_2)_2NH_2$ ~~or~~ $-(CH_2)_2Nalk^+X^-$ ~~radical~~, X ~~being a~~ halogen ~~atom~~ and alk ~~an~~ alkyl ~~radical containing~~ up to 8 carbon atoms,

Y ~~represents a~~ hydrogen ~~atom~~, ~~a~~ hydroxyl, ~~radical or a~~ halogen ~~atom or an~~ $-OSO_3H$ ~~radical~~ or ~~one of~~ the salt~~s~~ ~~of this radical~~,

W ~~represents a~~ hydrogen ~~atom~~ or ~~an~~ OH ~~radical~~,

Z ~~represents a~~ hydrogen ~~atom~~ or ~~a~~ methyl ~~radical~~,

~~as well as the~~ addition salt~~s~~ ~~with acids of the products of formula (I)~~.

2) ~~The~~ compound~~s~~ of ~~formula (I) defined in~~ claim 1 in which T ~~represents a~~ hydrogen ~~atom~~.

3) ~~The~~ compound~~s~~ of ~~formula (I) defined in~~ claim 1 ~~or 2~~ in which W ~~represents a~~ hydrogen ~~atom~~.

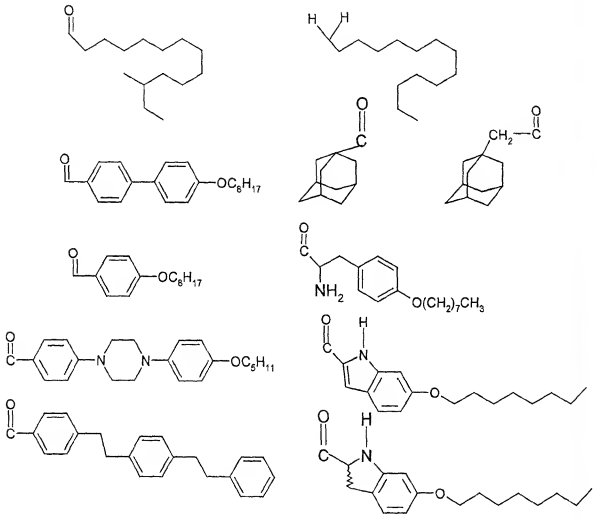
4) ~~A The~~ compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 3~~, in which Z ~~represents a~~ methyl ~~radical~~.

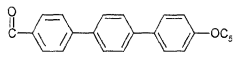
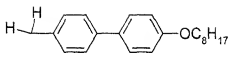
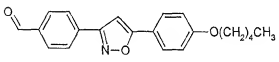
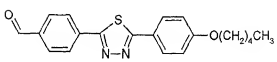
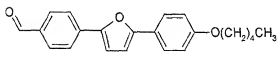
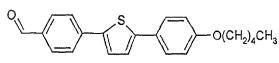
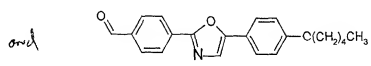
5) ~~A The~~ compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 4~~ in which Y ~~represents a~~ hydrogen ~~atom~~.

6) ~~A The~~ compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 5~~ in which R_3 ~~represents a~~ methyl ~~radical~~.

7) ~~A The~~ compound~~s~~ of ~~formula defined in any one of~~ claim~~s~~ 1 ~~to 6~~ in which R_4 ~~represents a~~ hydroxyl ~~radical~~.

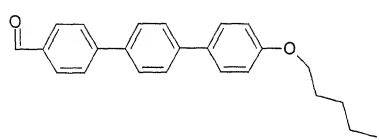
8) ~~The~~ A compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 7~~ in which R ~~represents a~~ is selected from the group consisting of



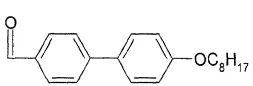
radical.

9) The compounds of formula (I) defined in claim 8, in which R represents a



chain.

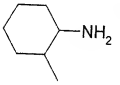
10) The compounds of formula (I) defined in claim 8, in which R represents a



chain.

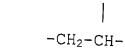
11) The compounds of formula (I) defined in any one of claims 1 to 10 in which R_1 is a hydrogen atom.

12) The compounds of formula (I) defined in any one of claims 1 to 11 in which R_2 is

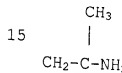


radical.

13) The compounds of formula (I) defined in any one of claims 1 to 11 in which R_2 is selected from the group consisting of

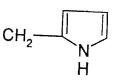


and

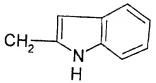


radical.

14) The compounds of formula (I) defined in any one of claims 1 to 11 in which R2 is



or

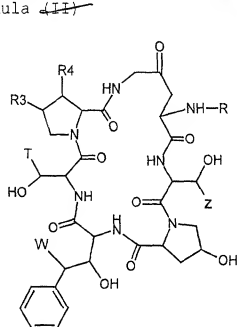


radical.

15) The compounds of formula (I) defined in any one of claims 1 to 14 selected from the group consisting of the names of which follow:

- 1-[4-[[(1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B), and
- trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

16) A process for the preparation of compounds of ~~formula (I) defined in any one~~ of claims 1 ~~to 15 characterized in that a~~ comprising reacting a compound of formula ~~(II)~~



(II)

~~in which~~ wherein R, R_3, R_4, T, Y, W and Z ~~retain their previous meaning,~~ are defined as in claim 1 is subjected to the action of an amine or amine derivative capable of introducing

~~the~~  ~~radical~~ in which R_1 and R_2 ~~retain their previous meaning~~ are defined as in claim 1 and ~~if desired~~ optionally to the action of

a reducing agent

and/or an amine functionalization agent,

and/or an acid ~~in order~~ to form the salt of the product of claim 1 ~~obtained~~,

and/or a separation agent of the different isomers obtained, ~~and the sought compound of formula (I) is thus obtained.~~

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

18) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.

(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau international

(43) Date de la publication internationale
14 décembre 2000 (14.12.2000)

PCT

(10) Numéro de publication internationale
WO 00/75177 A1

(51) Classification internationale des brevets⁷: C07K 7/56, A61K 38/12, A61P 31/10

(21) Numéro de la demande internationale:
PCT/FR00/01568

(22) Date de dépôt international: 8 juin 2000 (08.06.2000)

(25) Langue de dépôt: français

(26) Langue de publication: français

(30) Données relatives à la priorité:
99/07251 9 juin 1999 (09.06.1999) FR

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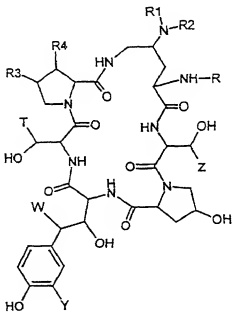
[Suite sur la page suivante]

(54) Title: ~~ECHINOCANDIN DERIVATIVES, METHOD FOR PREPARING SAME AND APPLICATION AS ANTIFUNGAL AGENTS~~

(54) Titre: NOUVEAUX DERIVES DE L'ECHINOCANDINE, LEUR PROCEDE DE PREPARATION ET LEUR APPLICATION COMME ANTIFONGIQUES



(I)

(57) Abstract: The invention concerns in all possible isomeric forms as well as their mixtures, compounds of formula (I) wherein: either R_1 represents H or CH_3 and R_2 represents cyclohexyl substituted by an amine, a (CH_2)b-C≡N radical; or R_1 and R_2 form with the nitrogen which bears them a cycle with 3, 4 or 5 carbons optionally substituted by an amine; R_3 represents hydrogen, methyl of hydroxyl; R_4 represents hydrogen or hydroxyl; R represents a linear, branched or cyclic chain; T represents hydrogen, methyl, CH_2CONH_2,

[Suite sur la page suivante]

WO 00/75177 A1

(74) **Mandataire:** TONNELLIER, Marie-José; Hoechst Marion Roussel, 102, route de Noisy, F-93235 Romainville Cedex (FR).

(81) **États désignés** *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.

(84) **États désignés** *(régional)*: brevet ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Publiée:
— *Avec rapport de recherche internationale.*
— *Avant l'expiration du délai prévu pour la modification des revendications, sera republiée si des modifications sont reçues.*

En ce qui concerne les codes à deux lettres et autres abréviations, se référer aux "Notes explicatives relatives aux codes et abréviations" figurant au début de chaque numéro ordinaire de la Gazette du PCT.

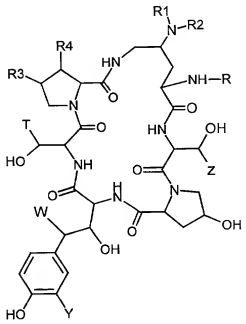
$CH_2C{\equiv}N$, a $(CH_2)_2NH_2$ or $(CH_2)_2Nalk^+X^-$ radical, X being halogen and alk an alkyl radical; Y represents hydrogen, hydroxyl, halogen or OSO_3H; W represents H or OH; Z represents H, CH_3. The compounds of formula (I) have antifungal properties.

(57) **Abrégé:** L'invention a pour objet sous toutes les formes d'isomères possibles ainsi que leurs mélanges, les composés de formule (I) dans lesquels ou bien R_1: H ou CH_3 et R_2 cyclohexyle substitué par une amine, un radical (CH_2)b-$C{\equiv}N$ ou bien R_1 et R_2 forment avec l'azote qui les porte un cycle à 3, 4 ou 5 carbones éventuellement substitué par une amine, R_3 hydrogène, méthyle ou hydroxyle, R_4 hydrogène ou hydroxyle, R représente une chaîne linéaire, ramifiée ou cyclique, T hydrogène, méthyle, CH_2CONH_2, $CH_2C{\equiv}N$, un radical $(CH_2)_2NH_2$ ou $(CH_2)_2Nalc^+X^-$, X halogène et alc alkyle, Y hydrogène, hydroxyle, halogène ou OSO_3H, W H ou OH, Z H, CH_3. Les composés de formule (I) présentent des propriétés antifongiques.

New derivatives of echinocandine, their preparation process and their use as antifungals.

The present invention relates to new derivatives of echinocandine, their preparation process and their use as antifungals.

A subject of the invention is, in all possible isomer forms as well as their mixtures, the compounds of formula (I):

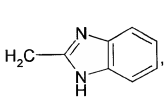


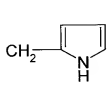
(I)

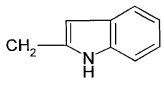
in which

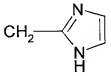
either R_1 represents a hydrogen atom or a methyl radical.

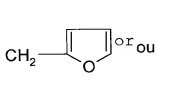
R_2 represents a cyclohexyl radical substituted by an amine, a $CH_2CH_2NHCH_3$ radical, a $CH_2CHCH_3NH_2$ radical, a

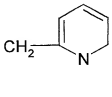












radical, a $CHCH_3CH_2NH_2$ radical, a $-(CH_2)aOH$ radical, a

representing an integer comprised between 1 and 8, a $(CH_2)_b$-C≡N radical, b representing an integer comprised between 1 and 8, a $CHCH_3C_6H_5$ radical, a (CH_2)-$C(CH_3)_2NHCOCF_3$ radical, a $CHCH_3(CH_2)_dOH$ radical, d representing an integer comprised between 1 and 8

or R_1 and R_2 form together with the nitrogen which carries them a ring with 3, 4 or 5 carbons optionally substituted by an amine

R_3 represents a hydrogen atom, a methyl or hydroxyl radical

R_4 represents a hydrogen atom or a hydroxyl radical

R represents a linear or branched or cyclic chain containing up to 30 carbon atoms, optionally containing one or more heteroatoms, one or more heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms optionally containing one or more heteroatoms and/or one or more heterocycles,

T represents a hydrogen atom, a methyl radical, a CH_2CONH_2 radical, $CH_2C{\equiv}N$, a $(CH_2)_2NH_2$ or $(CH_2)_2Nalk^+X^-$ radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO_3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

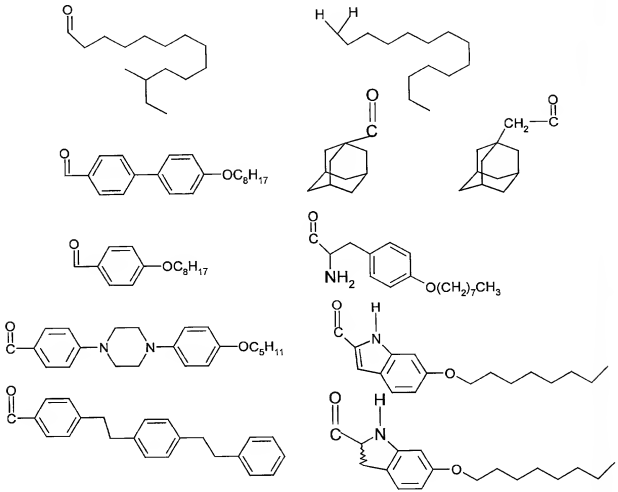
Z represents a hydrogen atom or a methyl radical,

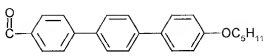
as well as the addition salts with acids of the products of formula (I).

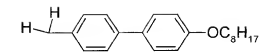
Among the addition salts with acids, there can be mentioned those formed with mineral acids, such as hydrochloric, hydrobromic, sulphuric or phosphoric acid or with organic acids such as formic, acetic, trifluoroacetic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic and aspartic acids, alkanesulphonic acids, such as methane or ethane sulphonic acid, arylsulphonic acids such as benzene or paratoluene sulphonic acids.

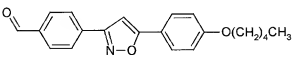
Among the preferred compounds of the invention, there can quite particularly be mentioned the compounds of formula I in which T represents a hydrogen atom, those in which W

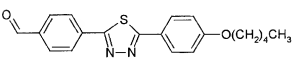
represents a hydrogen atom, those in which Z represents a methyl radical, those in which Y represents a hydrogen atom, those in which R_3 represents a methyl radical, those in which R_4 represents a hydroxyl radical, and those in which R represents a

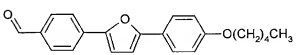


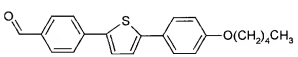


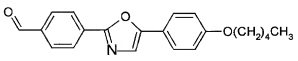






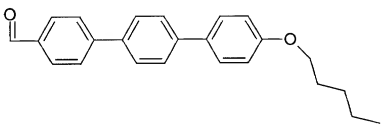




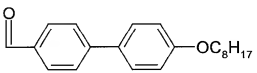


radical.

A most particular subject of the invention is the compounds of formula I in which R represents a

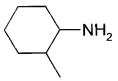


chain or a



chain.

Among the preferred compounds of the invention, there can be quite particularly mentioned the compounds of formula I in which R_1 is a hydrogen atom, those in which R_2 is a

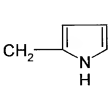


radical,

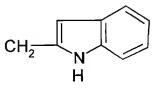
those in which R2 is a $-CH_2-CH-NH_2$ radical, a


$-CH-CH_2NH_2$ radical or a CH_2-C-NH_2 radical or also those in

which R_2 is a



or



radical

A most particular subject of the invention is the compounds of formula (I), the preparation of which is given hereafter in the experimental part and in particular the products of Examples 2 and 3.

The compounds of formula (I) have useful antifungal properties; they are in particular active on Candida albicans and other Candida such as Candida glabrata, krusei, tropicalis, pseudotropicalis, parapsilosis and Aspergillus fumigatus, Aspergillus flavus, Cryptococcus neoformans.

The compounds of formula (I) can be used as medicaments in man or animals, in particular to combat invasive candidosis in the immunosuppressed, digestive, urinary, vaginal or cutaneous candidosis, cryptococcosis, for example neuromeningeal, pulmonary or cutaneous cryptococcosis, bronchopulmonary and pulmonary aspergillosis and invasive

aspergillosis in the immunosuppressed.
The compounds of the invention can also be used in the prevention of mycotic illnesses in the congenital or acquired immunosuppressed.
The compounds of the invention are not limited to a pharmaceutical use, they can also be used as fungicides in fields other than the pharmaceutical field.

Therefore a subject of the invention is, as antifungal compounds, the compounds of formula (I) as well as their addition salts with acids.

A subject of the invention is also the compounds of formula (I), as medicaments.

A most particular subject of the invention is the pharmaceutical compositions containing as active ingredient at least one compound of formula (I) or one of its addition salts with pharmaceutically acceptable acids.
These compositions can be administrered by oral, rectal, parenteral route or by local route as a topical application on the skin and mucous membranes, but the preferred routes are the oral and parenteral routes.

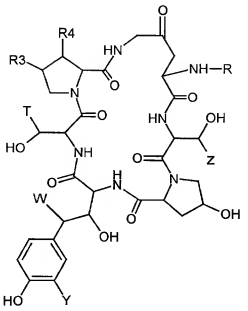
They can be solid or liquid and can be presented in the pharmaceutical forms commonly used in human medicine, such as for example, plain or sugar-coated tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods. The active ingredient or ingredients can be incorporated in the excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty matter of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

These compositions can also be presented in the form of a powder intended to be dissolved extemporaneously in an appropriate vehicle, for example apyrogenic sterile water.

The dose administered is variable according to the illness treated, the patient in question, the administration route and the product considered. It can be, for example,

comprised between 50 mg and 1 g per day by oral or parenteral route, in adults for the products of Examples 2 and 3.

A subject of the invention is also a preparation process characterized in that a compound of formula (II)



(II)

in which R, R_3, R_4, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or an amine derivative capable of introducing

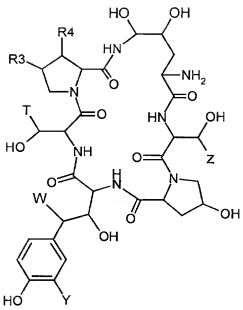
the  radical in which R_1 and R_2 retain their previous meaning and if desired is subjected to the action of a reducing agent

and/or of an amine functionalization agent,

and/or an acid in order to form the salt of the product obtained,

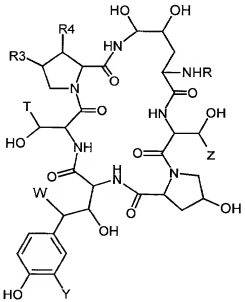
and/or a separation agent of the different isomers obtained, and the sought compound of formula (I) is thus obtained.

The compounds of formula (II) described and claimed in the Patent Application WO 99 29716 can be prepared according to a process characterized in that a compound of formula (III)



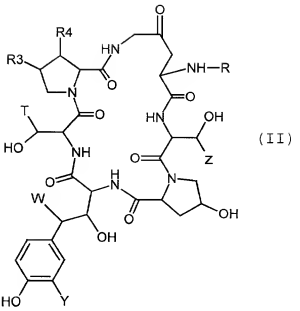
(III)

in which the different substituents retain their previous meaning is subjected to the action of an agent capable of replacing NH_2 with NHR, R retaining its previous meaning in order to obtain the compound of formula (IV)



(IV)

which is subjected to the action of trimethylsilyl iodide in order to obtain the corresponding compound of formula (II)



(II)

The following examples illustrate the invention without however limiting it.

Preparation 1: "nucleus" of deoxymulundocandine

2 g of deoxymulundocandine is dissolved in 20 ml of DMSO. This solution is poured into a suspension containing 120 g of Actinoplanes utahensis FH2264 in 870 ml of a KH2PO4, K2HPO4 buffer (pH: 6.8). The reaction mixture is maintained under agitation for 70 hours at 30°C. Filtration is carried out. The mycelium is washed with the phosphate buffer (pH: 6.8). The washing liquids and the filtrate are combined. The product obtained is chromatographed on a DIAION HP 20 resin and a product is obtained which is used as it is hereafter.

EXAMPLE 1: 1-[4-[((2S)-2-amino-2-methylethyl)-amino]-N2-[[4'-(octyloxy)[1,1'-biphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer A and isomer B).

Stage A: 1-[(4R,5R)-4,5-dihydroxy-N2-[[4'-(octyloxy)[1,1'-biphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine echinocandine B

1- Preparation of the ester

632 mg of 2,3,4,5,6 pentafluorophenol and 695 mg of N,N'-dicyclohexylcarbodiimide are added to 1 g of 4'-octyloxy-[1,1'-biphenyl]4-carboxylic acid in 22 ml of tetrahydrofuran, followed by agitation for 22 hours at ambient temperature and

filtration. The solvents are eliminated under reduced pressure, the residue is taken up in ether, agitated at approximately 35°C, followed by filtration, the solvent is evaporated followed by drying and 1.46 g of expected product is recovered, which is used as it is.

2- Coupling

677 mg of the deoxymulundocandine "nucleus" obtained in Preparation 1 is introduced into 16 ml of DMF. The solution obtained is agitated for 5 minutes and 793 mg of pentafluorophenyl 4'-(octyloxy)-[1,1'-biphenyl]-4-carboxylate obtained above is added. The reaction mixture is maintained under agitation and a nitrogen atmosphere for 24 hours. The reaction mixture is filtered and concentrated. The residue is taken up in ether, triturated, maintained under agitation for 25 minutes, separated, washed with ethyl ether, chromatographed on silica while eluting with a mixture of methylene chloride, methanol, water (86/13/1) then (80/20/1). The sought product is thus obtained. Yield 73%.

Stage B: 1-[N2-[[4'-(octyloxy)-[1,1'-biphenyl]-4-yl] carbonyl]-4-oxo-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B.

311 µl of trimethylsilyl iodide is added to a suspension containing 809 mg of the product of Stage A and 19 ml of acetonitrile. The reaction mixture is maintained under agitation for 15 minutes at 60°C and under a nitrogen atmosphere. The mixture is poured into a saturated solution of sodium thiosulphate followed by evaporation. The residue obtained is chromatographed on silica, eluting with a methylene chloride/methanol/water mixture 86/13/1. The sought product is obtained. Yield 55%.

Stade C: 1-[4-[((2S)-2-amino-2-methylethyl)amino]-N2-[[4'-(octyloxy)[1,1'-biphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer A and isomer B).

A solution containing 62.5 mg of (S)-(-)diaminopropane dihydrochloride, 2.25 ml of methanol, triethylamine in order to obtain a pH of 6, a few grains of activated siliporite and 150 mg of the product of the previous stage is agitated for a

few minutes at 20°C. 6 mg of $NaBH_3CN$ is introduced. Agitation is carried out for 15 hours at 20°C and after semi-preparative HPLC purification (eluent: CH_3CN,H_2OTFA(50-50-0.02), 11.5 mg of isomer A, 13 mg of isomer B are obtained.

EXAMPLE 2: 1-[4-[[(1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B).

By operating as previously starting from the nucleus of deoxymulundocandine prepared in Preparation 1 and obtaining 1-[(4R,5R)-4,5-dihydroxy-N2-[[4''-(pentyloxy)[1,1': 4',1''-terphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B as intermediate product and the corresponding 4-oxo derivative, the sought product was obtained. Isomer A = 7.4 mg, isomer B = 1.2 mg.

EXAMPLE 3: Trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

By operating as previously, starting from 166 mg of the 4-oxo derivative prepared above and 78 mg of (1R, 2R)1-2-diaminocyclohexane, 462 mg of crude product is obtained which is chromatographed on silica eluting with a methylene chloride, methanol, H_2O, acetic acid mixture 86/13/2/1. 100 mg of product is obtained which is purified by semi-preparative HPLC again with a CH_3CN/H_2O/TFA mixture = 50/50/0.1. 55 mg of isomer A, 5.2 mg of isomer B are obtained.

EXAMPLE 4: 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

By operating as previously, the sought product was obtained.

EXAMPLE: Pharmaceutical composition:

Tablets were prepared containing:

- Product of Example 3 isomer A..... 150 mg

- Excipient s.q.f. ..... 1 g
(Detail of excipient: starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY

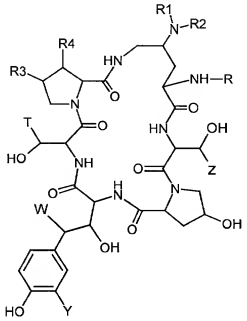
A - Inhibition of the glucan synthase of Candida albicans.
Candida albicans membranes were purified according to the process described by Tang et al Antimicrob. Agents Chemother 35, 99-103, 1991. 22.5 µg of membrane proteins are incubated in a mixture of 2Mm of 14C-UDP glucose (specific activity = 0.34 mCi./mmol, 50 µg of α-amylase, 1Mm of dithiotreitol (DTT), 1Mm EDTA, 100Mm NaF, 7µM of GTP-γ-S, 1M of sucrose and 50Mm of Tris-HCL (pH 7.8) in a volume of 100µl. The medium is incubated at 25°C for 1 hour and the reaction is terminated by adding TCA at a final concentration of 5%. The reaction mixture is transferred onto a pre-humidified glass fibre filter. The filter is washed, dried and its radioactivity is counted.
Mulundocandine is used as a positive control.
Control of the vehicle is carried out with the same quantity of 1% DMSO. The results obtained show that in this test the products of the invention show a good activity in particular the products of Example 3 isomer A.

B - activity on the Aspergillus fumigatus enzyme.
The enzyme is prepared according to the process of Beaulieu et al.(Antimicrob. Agents Chenother 38, 937-944, 1994.
The protocol used is identical to the protocol described above for the enzyme of Candida albicans except that dithiotreitol is not used in the reaction mixture.

In this test the products show a good activity.

CLAIMS

1) In all possible isomer forms as well as their mixtures, the compounds of formula (I):

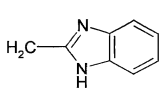


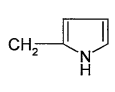
(I)

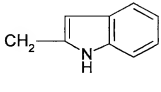
in which

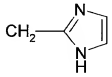
either R_1 represents a hydrogen atom or a methyl radical.

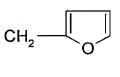
R_2 represents a cyclohexyl radical substituted by an amine, a $CH_2CH_2NHCH_3$ radical, a $CH_2CHCH_3NH_2$ radical, a



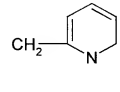








or ou



radical, a $CHCH_3CH_2NH_2$ radical, a -(CH2)aOH radical, a representing an integer comprised between 1 and 8, a $(CH_2)b$-C≡N radical

b representing an integer comprised between 1 and 8, a $CHCH_3C_6H_5$ radical, a (CH_2)-$C(CH_3)_2NHCOCF_3$ radical, a

$CHCH_3(CH_2)dOH$ radical, d representing an integer comprised between 1 and 8

or R_1 and R_2 together with the nitrogen which carries them form a ring with 3, 4 or 5 carbons optionally substituted by an amine

R3 represents a hydrogen atom, a methyl or hydroxyl radical

R_4 represents a hydrogen atom or a hydroxyl radical

R represents a linear or branched or cyclic chain containing up to 30 carbon atoms, optionally containing one or more heteroatoms, one or more heterocycles or a linear, branched or cyclic acyl radical containing up to 30 carbon atoms optionally containing one or more heteroatoms and/or one or more heterocycles,

T represents a hydrogen atom, a methyl radical, a CH_2CONH_2, $CH_2C{\equiv}N$ radical, a $(CH_2)_2NH_2$ or $(CH_2)_2Nalk^+X^-$ radical, X being a halogen atom and alk an alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom or an OSO_3H radical or one of the salts of this radical,

W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical,

as well as the addition salts with acids of the products of formula (I).

2) The compounds of formula (I) defined in claim 1 in which T represents a hydrogen atom.

3) The compounds of formula (I) defined in claim 1 or 2 in which W represents a hydrogen atom.

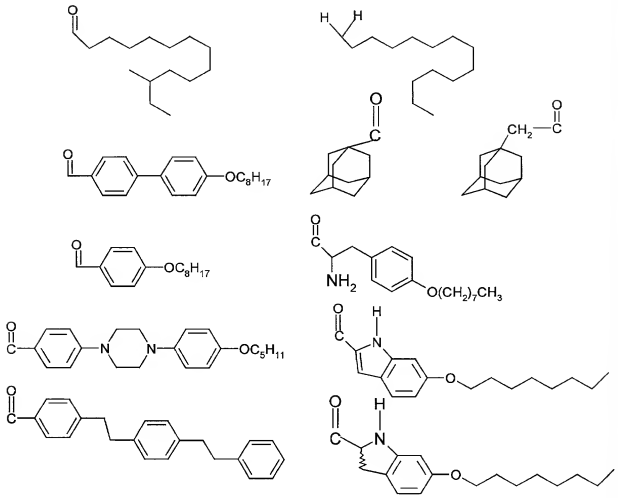
4) The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

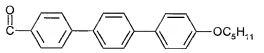
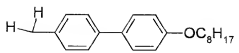
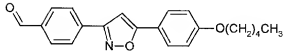
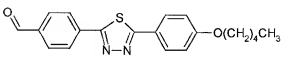
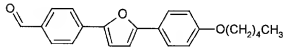
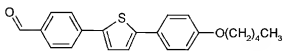
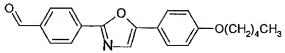
5) The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

6) The compounds of formula (I) defined in any one of claims 1 to 5 in which R_3 represents a methyl radical.

7) The compounds of formula defined in any one of claims 1 to 6 in which R_4 represents a hydroxyl radical.

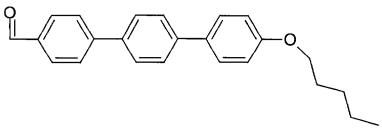
8) The compounds of formula (I) defined in any one of claims 1 to 7 in which R represents a



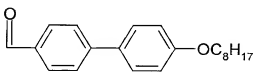
radical.

9) The compounds of formula (I) defined in claim 8, in which R represents a



chain.

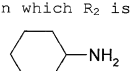
10) The compounds of formula (I) defined in claim 8, in which R represents a



chain.

11) The compounds of formula (I) defined in any one of claims 1 to 10 in which R_1 is a hydrogen atom.

12) The compounds of formula (I) defined in any one of claims 1 to 11 in which R_2 is a



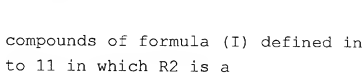
radical.

13) The compounds of formula (I) defined in any one of claims 1 to 11 in which R_2 is a

$-CH_2-CH(CH_3)-NH_2$ radical, a $-CH(CH_3)-CH_2NH_2$ radical or a

$CH_2-C(CH_3)_2-NH_2$ radical.

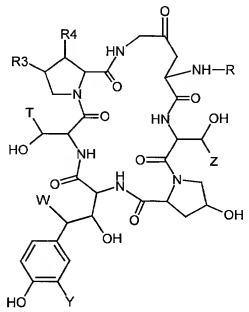
14) The compounds of formula (I) defined in any one of claims 1 to 11 in which R2 is a



radical.

15) The compounds of formula (I) defined in any one of claims 1 to 14 the names of which follow:
- 1-[4-[[(1H-benzimidazol-2-yl)-methyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B),
- trans 1-[4-[(2-aminocyclo-hexyl)-amino]-N2-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate (isomer A).

16) Process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15 characterized in that a compound of formula (II)



(II)

in which R, R_3, R_4, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or amine derivative capable of introducing

the  radical in which R_1 and R_2

retain their previous meaning and if desired to the action of a reducing agent
and/or an amine functionalization agent,
and/or an acid in order to form the salt of the product obtained,
and/or a separation agent of the different isomers obtained, and the sought compound of formula (I) is thus obtained.

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

18) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

[X] Declaration Submitted with Initial Filing OR [ ] Declaration Submitted after Initial Filing

Attorney Docket Number	146.1374
First Named Inventor	J.L. LALANNE et al
COMPLETE IF KNOWN	
Application Number	PCT/FR00/01567
Filing Date	June 8, 2000
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

NOVEL CANDIDA ALBICANS GENES AND PROTEINS CODED BY THESE GENES

(Title of the Invention)

the specification of which

[ ] is attached hereto

OR

[X] was filed on (MM/DD/YYYY) June 8, 2000 as United States Application Number or PCT International

Application Number PCT/FR00/01567 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
99/07250	France	6/9/99	[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]
			[ ]	[ ]	[ ]

[ ] Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

[ ] Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

Please type a plus sign (+) inside this box → +

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian	19,683		
Jordan B. Bierman	18,629		
Donald C. Lucas	31,275		
Bierman, Muserlian and Lucas	18,818		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name: Bierman, Muserlian and Lucas

Address:

Address: 600 Third Avenue

City: New York | State: New York | ZIP: 10016

Country: U.S.A. | Telephone: (212) 661-8000 | Fax: (212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
JEAN	L	LALANNE	

Inventor's Signature: [signature] Date: December 17th 2001

Residence: City: Fontenay sous Bois | State: | Country: France | Citizenship: FR

Post Office Address:

Post Office Address: 110. avenue du Marechal

City: Fontenay sous Bois | State: | Zip: F-94120 | Country: France

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

Please type a plus sign (+) inside this box → [+] 146.1374

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any:							☐ A petition has been filed for this unsigned inventor
Given Name	CORINNE	Middle Initial		Family Name	ROCHER	Suffix e.g. Jr.	
Inventor's Signature	[signature]					Date	December 13, 2001
Residence: City	Pairs	State		Country	France	Citizenship	FR
Post Office Address							
Post Office Address	3, rue Elisa Lemonnier						
City	Paris	State		Zip	F-75012	Country	France

Name of Additional Joint Inventor, if any:							☐ A petition has been filed for this unsigned inventor
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:							☐ A petition has been filed for this unsigned inventor
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:							☐ A petition has been filed for this unsigned inventor
Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

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